Remarks

Courtesies extended to Applicants' representative in the personal interview held on November 21, 2002, are acknowledged with appreciation.

As discussed at the personal interview, the present invention provides methods for modulating expression of exogenous genes in isolated cells containing a defined DNA construct (*i.e.*, claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, and 57-71). DNA constructs contemplated herein comprise an exogenous gene under the control of a (modified or unmodified) response element plus a modified ecdysone receptor which, in the presence of an appropriate ligand, binds to the response element. Optionally, a second receptor member is included that acts as a silent partner for the modified ecdysone receptor. The invention method comprises providing to an isolated cell containing the construct an effective amount of a ligand(s) for the modified ecdysone receptor, wherein the ligand(s) is not normally present in the cell. The presence of ligand for the modified ecdysone receptor (and optionally, the presence of a silent partner) promotes the formation of ligand-receptor complexes that interact with corresponding response elements, thereby modulating expression of exogenous genes.

The present invention further provides methods of gene regulation in mammalian subjects (*i.e.*, claims 72-77). DNA constructs contemplated for use in such methods are analogous to those described above with respect to methods of use employing isolated cells.

Invention methods are useful in a wide variety of applications. Modulation of exogenous gene expression is desirable in numerous isolated cell populations ranging from transiently modified cells to stably transformed cell lines. For example, invention methods can advantageously be employed in *in vitro* cellular expression systems to regulate expression of a recombinant expression product. Similarly, host cells and other recombinant cell types can benefit from invention methods for modulating the expression of an exogenous gene. In addition, *in vivo* uses of the same expression systems are contemplated in mammalian subjects.

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Claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 were pending before this response. By this response, claims 1, 4, 5, 11, 22-24, 47-52, 54, 58, 59, 61, and 67-77 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and the original claims. Applicants respectfully submit that the amendments presented herein place the application in condition for allowance or, at a minimum, reduce the issues for appeal. Accordingly, entry of the amendments is respectfully requested. Attached hereto is a marked-up version of the changes made to the claims, labeled APPENDIX A.

Accordingly, claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 remain currently pending. For the Examiner's convenience, a clean copy of all pending claims as they will stand upon entry of the proposed amendments is also provided in APPENDIX B.

The rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention, is respectfully traversed. Applicants respectfully submit that in view of the specification, one would have no reason to doubt that Applicants had possession of the claimed methods for modulating gene expression. Applicants' method requires providing one or more ligands for a modified ecdysone receptor, which receptor binds to a response element that controls expression of a gene. Each element of invention methods for modulating the expression of exogenous genes has been fully disclosed in the specification.

Invention methods, as defined by claim 1, require providing to an isolated cell an effective amount of one or more ligands for a modified ecdysone receptor, wherein said ligand(s) are not normally present in the cell. The cell contains a DNA construct composed of an exogenous gene under the control of a defined response element, *i.e.*, an element to which a modified ecdysone receptor binds; and a corresponding modified ecdysone receptor that binds to the response element in the presence of a ligand.

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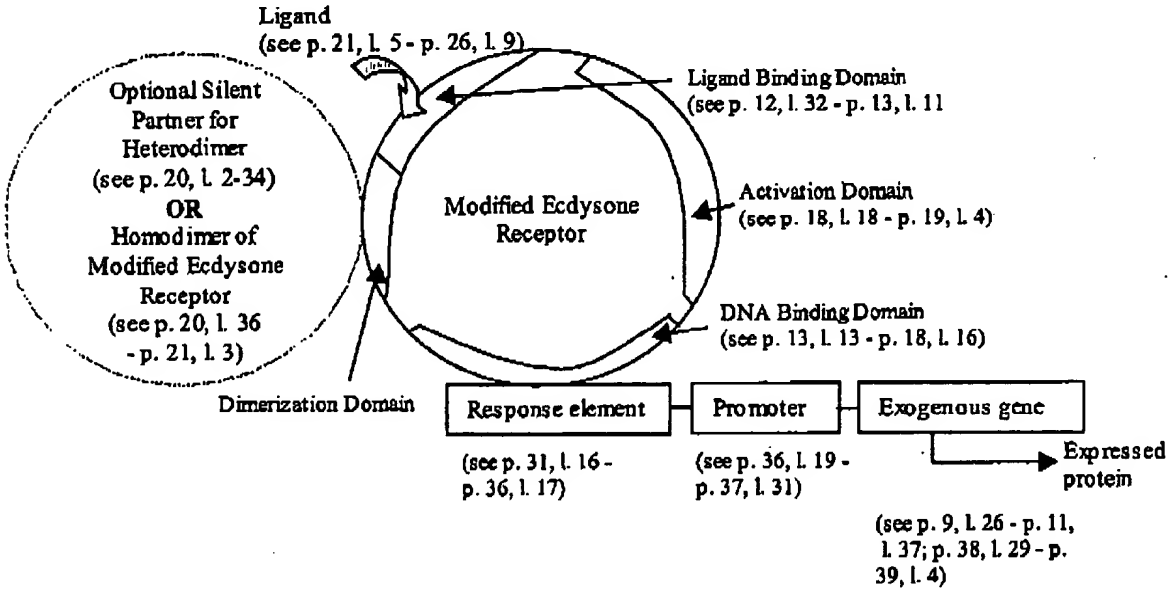
As discussed during the personal interview, each component contemplated for use in the present claims is explicitly disclosed in the specification. Thus, one of skill in the art would have no reason to doubt that Applicants were in possession of the claimed invention at the time of filing. The following schematic illustrates all required components of the invention, and identifies substantial exemplary support in the specification for every required component.



Thus, each element of the present claims is described in detail in the specification as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection of the claims under 35 U.S.C. § 112, first paragraph.

The rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for the method as claimed, is respectfully traversed. Applicants respectfully submit that the specification as filed enables any person skilled in the art to make and use the invention commensurate in scope with the present claims.

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One of skill in the art could readily follow the specific teachings of the specification to modulate expression of an exogenous gene as claimed. Each element required by the present methods is fully described by the specification as filed, as noted above. Methods for creating DNA constructs encoding the contemplated receptor(s) and the exogenous gene(s) to be regulated, and for transfecting cells with these constructs, are standard routine molecular biological manipulations clearly known to one of skill in the art at the time of filing. Moreover, the specification provides additional guidance on the use of these standard procedures (see, *e.g.*, specification at page 38, line 29 through page 46, line 20). Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection of the claims under 35 U.S.C. § 112, first paragraph.

However, in further efforts to advance prosecution and reduce the issues for appeal, independent claims 1, 22-24, 50, and 67-77 have been amended to further clarify Applicants' invention. In particular, the claims have been amended to reiterate that the response element binds to the modified ecdysone receptor defined in each claim. In addition, claims reciting a response element have been amended to further define the response element with respect to both its structural and functional characteristics. The response element controlling expression of the associated gene (a) has about 12-20 base pairs, (b) binds to the modified ecdysone receptor defined in the claim, and (c) does not bind to farnesoid X receptor (FXR). Thus, it is respectfully submitted that the specific response element and the corresponding modified ecdysone receptor of each claim is clear and readily available to one of skill in the art.

As further discussed during the personal interview, a silent partner, *i.e.*, a receptor partner other than a modified ecdysone receptor, is optional. The modified ecdysone receptor of the invention is capable of functioning as either a heterodimer or a homodimer (see, for example, specification at page 31, lines 20-32). In embodiments where the invention-modified ecdysone receptor functions as a heterodimer, its receptor partner is a receptor other than a modified ecdysone receptor, *i.e.*, a silent partner. In embodiments where the invention-modified ecdysone receptor functions as a homodimer, its receptor partner is a modified ecdysone receptor.

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The invention receptor is a modified ecdysone receptor composed of domains from various members of the steroid/thyroid hormone receptor superfamily, also known as nuclear receptors (see, for example, specification at page 15, lines 1-9). It is one of the benefits of the present invention that unique properties are imparted to the ecdysone receptor upon conversion into the chimeric modified receptor. Such unique properties include, for example, functional homodimerization. The specification clearly contemplates such homodimeric species of the modified ecdysone receptors, which do not require any additional dimer partner (see, for example, specification at page 20, line 36, through page 21, line 3). Thus, a receptor other than a modified ecdysone receptor, *i.e.*, a silent partner, is clearly optional and not a requirement of the present claims.

For all of the reasons cited above, it is respectfully submitted that the present claims meet all requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of both the written description and enablement rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

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Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Appendices A and B

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APPENDIX A – ALTERED CLAIMS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 4, 5, 11, 22-24, 47-52, 54, 58, 59, 61, and 67-77 have been amended as follows:

1. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) [~~a DNA construct comprising said exogenous gene under the control of a response element to which the modified ecdysone receptor of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR); and~~

~~(ii)~~] a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a [~~receptor capable of acting as a~~] silent partner therefor, binds to **a** [~~said~~] response element, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** [~~capable of binding~~] an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein**, which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; **and**

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

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said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

4. (Amended) A method according to claim 1 wherein the DNA-binding domain of said modified ecdysone receptor is derived from a **nuclear receptor** [~~member of the steroid/thyroid hormone superfamily of receptors~~].

5. (Amended) A method according to claim 1 wherein said activation domain is obtained from a **nuclear receptor** [~~member of the steroid/thyroid hormone superfamily of receptors~~].

11. (Amended) A method according to claim 1, wherein said [~~receptor capable of acting as a~~] silent partner is RXR.

22. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) [~~a DNA construct comprising an exogenous gene under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);~~

~~(ii)~~] DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a [~~receptor capable of acting as a~~] silent partner therefor, binds to **a** [~~said~~] response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** [~~capable of binding~~] an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, **which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native

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ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR); and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified ecdysone receptor.

23. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of a response element **[~~to which a modified ecdysone receptor binds~~]**, wherein said response element **(a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to [~~has substantially no binding affinity for~~]** farnesoid X receptor (FXR), said method comprising introducing into said cell:

a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to [~~capable of binding~~]** an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, **which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said receptor, in combination with a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said response element, activating transcription therefrom.

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24. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) ~~[a DNA construct encoding said recombinant product under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), and~~ ~~(ii)~~] DNA encoding a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** ~~[capable of binding]~~ an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; **and**

(ii) a DNA construct encoding said recombinant product under the control of a response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified ecdysone receptor, and optionally a ~~[receptor capable of acting as a]~~ silent partner for said modified ecdysone receptor.

47. (Amended) A method according to claim 1, wherein said ~~[receptor capable of acting as a]~~ silent partner is present.

48. (Amended) A method according to claim 47 wherein said ~~[receptor capable of acting as a]~~ silent partner is ultraspiracle.

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49. (Amended) A method according to claim 1 wherein said modified ecdysone receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements.

50. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said ecdysone response element, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

51. (Amended) A method according to claim 50, wherein said **[~~receptor capable of acting as a~~]** silent partner is present.

52. (Amended) A method according to claim 51, wherein said **[~~receptor capable of acting as a~~]** silent partner is ultraspiracle.

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54. (Amended) A method according to claim 51, wherein said [~~receptor capable of acting as a~~] silent partner is RXR.

58. (Amended) A method according to claim 50 wherein the DNA-binding domain of said modified receptor is derived from a **nuclear receptor** [~~member of the steroid/thyroid hormone superfamily of receptors~~].

59. (Amended) A method according to claim 50 wherein said activation domain is derived from a **nuclear receptor** [~~member of the steroid/thyroid hormone superfamily of receptors~~].

61. (Amended) A method according to claim 50, wherein said ecdysone response element **does not bind to** [~~has substantially no binding affinity for~~] farnesoid X receptor (FXR).

67. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a [~~receptor capable of acting as a~~] silent partner therefor, binds to said ecdysone response element, wherein said modified receptor **does not bind to** [~~has substantially no binding affinity for~~] endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** [~~capable of binding~~] an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** [~~has substantially no binding affinity for~~] endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said

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activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified receptor.

68. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said cell:

a modified receptor, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in combination with a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

69. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of an ecdysone response element, and

(ii) DNA encoding a modified receptor, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response

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elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified receptor, and optionally a **[~~receptor capable of acting as a~~]** silent partner for said modified receptor.

70. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said ecdysone response element wherein said modified receptor has substantially no constitutive activity in mammalian cells, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

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said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

71. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a ~~[receptor capable of acting as a]~~ silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has an altered DNA binding specificity relative to the wildtype receptor from which it is derived, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** ~~[capable of binding]~~ an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, **which binds to said ecdysone response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

72. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) ~~[a DNA construct comprising said exogenous gene under the control of a response element to which the modified ecdysone receptor of (ii) binds, wherein said response element has substantially no binding affinity for~~

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~~farnesoid X receptor (FXR); and~~

~~(ii)~~] a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a [~~receptor capable of acting as a~~] silent partner therefor, binds to a [~~said~~] response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** [~~capable of binding~~] an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, **which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; **and**

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

said method comprising providing to said subject an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

73. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) [~~a DNA construct comprising an exogenous gene under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);~~

~~(ii)~~] DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a [~~receptor capable of acting as a~~] silent partner therefor, binds to a [~~said~~] response element, and

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wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** **~~[capable of binding]~~** an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein**, which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(ii). a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR); and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified ecdysone receptor.

74. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of a response element **~~[to which the modified ecdysone receptor described below binds]~~**, wherein said response element **(a) has about 12-20 base pairs, (b) binds to a modified ecdysone receptor, and (c) does not bind to** **~~[has substantially no binding affinity for]~~** farnesoid X receptor (FXR), said method comprising introducing into said subject:

a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain **that binds to** **~~[capable of binding]~~** an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein**, which binds to said response element**; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

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wherein said modified ecdysone receptor, in combination with a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said response element, activating transcription therefrom.

75. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said **ecdysone** response element, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to said subject an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

76. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor,

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and optionally in the further presence of a **[~~receptor capable of acting as a~~]** silent partner therefor, binds to said ecdysone response element, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified receptor.

77. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said subject:

a modified receptor, wherein said modified receptor **does not bind to** **[~~has substantially no binding affinity for~~]** endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain **that binds to** **[~~capable of binding~~]** an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain **binds to said ecdysone response element but not to** **[~~has substantially no binding affinity for~~]** endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

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wherein said modified receptor, in **the presence of** [~~**connection with**~~] a ligand therefor, and optionally in the further presence of a [~~**receptor capable of acting as a**~~] silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

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APPENDIX B – COMPLETE SET OF PENDING CLAIMS

1. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to a response element, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

3. (Reiterated) A method according to claim 1 wherein said modified ecdysone receptor is further characterized as having substantially no constitutive activity in mammalian cells.

4. (Amended) A method according to claim 1 wherein the DNA-binding domain of said modified ecdysone receptor is derived from a nuclear receptor.

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5. (Amended) A method according to claim 1 wherein said activation domain is obtained from a nuclear receptor.

6. (Reiterated) A method according to claim 1 wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

7. (Reiterated) A method according to claim 6 wherein said modified ecdysone receptor is VpEcR, VgEcR or GecR.

8. (Reiterated) A method according to claim 7 wherein said modified ecdysone receptor is VgEcR having the amino acid sequence set forth in SEQ ID NO:5.

9. (Reiterated) A method according to claim 1 wherein said modified ecdysone receptor is present primarily in the form of a homodimer.

11. (Amended) A method according to claim 1, wherein said silent partner is RXR.

12. (Reiterated) A method according to claim 11 wherein said RXR is exogenous to said cell.

13. (Reiterated) A method according to claim 1 wherein said response element is a modified response element which comprises, in any order, a first half-site and a second half-site separated by a spacer of 0-5 nucleotides;

wherein said first half-site has the sequence:

-RGBNNM-,

wherein

each R is independently selected from A or G;

each B is independently selected from G, C, or T;

each N is independently selected from A, T, C, or G; and

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each M is independently selected from A or C;

with the proviso that

at least 4 nucleotides of each -RGBNNM- group of nucleotides are identical with the nucleotides at comparable positions of the sequence -AGGTCA-; and

said second half-site is obtained from a glucocorticoid receptor subfamily response element.

15. (Reiterated) A method according to claim 1 wherein said ligand is a naturally occurring ecdysone, an ecdysone-analog or an ecdysone mimic.

16. (Reiterated) A method according to claim 15 wherein said naturally occurring ecdysone is α-ecdysone or β-ecdysone.

17. (Reiterated) A method according to claim 15 wherein said ecdysone analog is ponasterone A, ponasterone B, ponasterone C, 26-iodoponasterone A, muristerone A, inokosterone or 26-mesylinokosterone.

18. (Reiterated) A method according to claim 15 wherein said ecdysone mimic is 3,5-di-tert-butyl-4-hydroxy-N-isobutyl-benzamide, 8-O-acetylharpagide, a 1,2-diacyl hydrazine, an N'-substituted-N,N'-disubstituted hydrazine, a dibenzoylalkyl cyanohydrazine, an N-substituted-N-alkyl-N,N-diaroyl hydrazine, an N-substituted-N-acyl-N-alkyl, carbonyl hydrazine or an N-aroyl-N'-alkyl-N'-aroyl hydrazine.

19. (Reiterated) A method according to claim 1 wherein said exogenous gene is a wild type gene and/or gene of interest.

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20. (Reiterated) A method according to claim 19 wherein said wild type gene encodes products:

the substantial absence of which leads to the occurrence of a non-normal state in said cell; or

a substantial excess of which leads to the occurrence of a non-normal state in said cell.

21. (Reiterated) A method according to claim 19 wherein said gene of interest encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

22. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to a response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR); and

(iii) one or more ligands for said modified ecdysone receptor;

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said method comprising subjecting said cell to conditions suitable to induce expression of said modified ecdysone receptor.

23. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of a response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR), said method comprising introducing into said cell:

a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said receptor, in combination with a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said response element, activating transcription therefrom.

24. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) DNA encoding a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived

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from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

(ii) a DNA construct encoding said recombinant product under the control of a response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified ecdysone receptor, and optionally a silent partner for said modified ecdysone receptor.

39. (Reiterated) A method according to claim 13, wherein said first half-site is obtained from an ecdysone response element and said second half-site is obtained from a glucocorticoid response element, a mineralocorticoid response element, a progesterone response element or an androgen response element.

40. (Reiterated) A method according to claim 39, wherein said second half-site is obtained from a glucocorticoid response element.

47. (Amended) A method according to claim 1, wherein said silent partner is present.

48. (Amended) A method according to claim 47 wherein said silent partner is ultraspiracle.

49. (Amended) A method according to claim 1 wherein said modified ecdysone receptor does not bind to endogenous response elements.

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50. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

51. (Amended) A method according to claim 50, wherein said silent partner is present.

52. (Amended) A method according to claim 51, wherein said silent partner is ultraspiracle.

53. (Reiterated) A method according to claim 50, wherein said cell is a mammalian cell.

54. (Amended) A method according to claim 51, wherein said silent partner is RXR.

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55. (Reiterated) A method according to claim 54, wherein said RXR is exogenous to said cell.

57. (Reiterated) A method according to claim 50 wherein said modified receptor is further characterized as having substantially no activity in mammalian cells.

58. (Amended) A method according to claim 50 wherein the DNA-binding domain of said modified receptor is derived from a nuclear receptor.

59. (Amended) A method according to claim 50 wherein said activation domain is derived from a nuclear receptor.

60. (Reiterated) A method according to claim 50 wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

61. (Amended) A method according to claim 50, wherein said ecdysone response element does not bind to farnesoid X receptor (FXR).

62. (Reiterated) A method according to claim 50 wherein said modified receptor has an altered DNA binding specificity relative to the wildtype receptor from which it is derived.

63. (Reiterated) A method according to claim 50 wherein said modified receptor is present primarily in the form of a homodimer.

64. (Reiterated) A method according to claim 50 wherein said exogenous gene is a wild type gene and/or gene of interest.

65. (Reiterated) A method according to claim 64 wherein said wild type gene encodes products:

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the substantial absence of which leads to the occurrence of a non-normal state in said cell; or

a substantial excess of which leads to the occurrence of a non-normal state in said cell.

66. (Reiterated) A method according to claim 64 wherein said gene of interest encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

67. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified receptor.

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68. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said cell:

a modified receptor, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in combination with a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

69. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of an ecdysone response element, and

(ii) DNA encoding a modified receptor, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

growing said host cells in suitable media; and

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inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified receptor, and optionally a silent partner for said modified receptor.

70. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element wherein said modified receptor has substantially no constitutive activity in mammalian cells, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

71. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has an altered DNA

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binding specificity relative to the wildtype receptor from which it is derived, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said ecdysone response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

72. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to a response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR);

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said method comprising providing to said subject an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

73. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to a response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR); and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified ecdysone receptor.

74. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of a response element, wherein said response element (a) has about 12-20 base pairs, (b) binds to a modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR), said method comprising introducing into said subject:

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a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response element; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said modified ecdysone receptor, in combination with a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said response element, activating transcription therefrom.

75. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to said subject an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

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76. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified receptor.

77. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said subject:

a modified receptor, wherein said modified receptor does not bind to endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain that binds to an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain binds to said ecdysone response element but not to endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

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wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

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